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Validation of ROPScore to predict retinopathy of prematurity among very low birth weight preterm infants in a southern Brazilian population

Validação de um escore (ROPScore) capaz de prever a ocorrência da retinopatia da prematuridade em prematuros de baixo peso no sul do Brasil

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RESUMO | Objetivos: Avaliar a sensibilidade, especificidade e os valores de pontos de corte do ROPScore, um escore baseado em fatores de risco cumulativos capaz de prever a ocorrência da retinopatia da prematuridade em prematuros de baixo peso no sul do Brasil. **Métodos:** Estudo retrospectivo por meio de análise de prontuários de todos os prematuros com peso ao nascer ≤1500g e/ou idade gestacional ≤32 semanas selecionados para retinopatia da prematuridade em duas instituições brasileiras entre agosto de 2009 e dezembro de 2015. **Resultados:** O estudo incluiu 322 pacientes. A média do peso ao nascer foi de 1181,8 ± 292,5 gr e a idade gestacional média foi de 29,5 ± 2,3 semanas. A incidência de retinopatia da prematuridade em qualquer estágio e retinopatia da prematuridade grave foi de 68,3% e 17%, respectivamente. Os valores do ROPScore variaram de 8,7 a 19,9. O melhor ponto de corte para sensibilidade e especificidade foi estabelecido em 11 para retinopatia da prematuridade em qualquer estágio e 14,5 para retinopatia da prematuridade grave. Para retinopatia da prematuridade em qualquer estadiamento, o ROPScore apresentou sensibilidade de 98,6% (95%IC 97,9-99,3) e especificidade de 35,3% (95%IC 32,3-38,3), valor preditivo positivo (VPP) de 76,6% (95%IC 74,0-79,2) e valor preditivo negativo de 92,3% (IC95% 90,6-94,0). Para retinopatia da prematuridade grave, foi registrada sensibilidade de 100%, especificidade de 57,3% (95%IC 54,2-60,4), valor preditivo positivo de 22% (95%IC 19,4-24,6) e valor preditivo negativo de 100%. Os pontos de corte identificaram corretamente todos os pacientes que desenvolveram qualquer estágio ou retinopatia da prematuridade grave no estudo. **Conclusão:** O ROPScore foi importante para detectar pacientes prematuros com risco de retinopatia da prematuridade. Nesta população, o ROPScore detectou todos os pacientes em risco para qualquer retinopatia da prematuridade em estágio e retinopatia da prematuridade grave. Este estudo mostrou valores semelhantes aos descritos anteriormente, validando com sucesso a ROPScore para detecção precoce de retinopatia da prematuridade em prematuros de muito baixo peso.

Descritores: Recém-nascido prematuro; Retinopatia da prematuridade; Baixo peso ao nascer; Fatores de risco; ROPScore; Índice de gravidade de doença; Cegueira

ABSTRACT | Purposes: To evaluate the sensitivity, specificity, and cutoff points for the ROPScore, which is based on cumulative risk factors for the prediction of retinopathy of prematurity (ROP), in a population of very low birth weight (BW) preterm infants in southern Brazil. **Methods:** The medical records of all preterm infants with a very low birth weight ≤1,500 g and/or gestational age ≤32 weeks screened for retinopathy of prematurity in two Brazilian institutions between August 2009 and December 2015 were retrospectively reviewed. ROPScores were calculated using birth weight and gestational age, the use of oxygen therapy with mechanical ventilation, and weight gain proportional to birth weight, as measured at postpartum week six and the need for blood transfusions. **Results:** The study cohort included 322 infants with a mean birth weight of 1181.8 ± 292.5 g and mean gestational age of 29.5 ± 2.3 weeks. The incidences of any stage of retinopathy of prematurity and severe retinopathy of prematurity were 68.3% and 17%, respectively. ROPScore values ranged from 8.7 to 19.9. The best cutoff point for sensitivity and specificity

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was 11 for any stage of retinopathy of prematurity and 14.5 for severe retinopathy of prematurity. For any stage of retinopathy of prematurity, the sensitivity and specificity of the ROPScores were 98.6% (95% confidence interval = 97.9%-99.3%) and 35.3% (95% confidence interval= 32.3%-38.3%), with a positive predictive value of 76.6% (95% confidence interval= 74.0%-79.2%) and a negative predictive value of 92.3% (95% confidence interval= 90.6%-94.0%). For severe retinopathy of prematurity, the sensitivity was 100% and specificity was 57.3% (95% confidence interval= 54.2%-60.4%), with positive predictive value of 22% (95% confidence interval= 19.4%-24.6%) and negative predictive value of 100%. The cutoff points correctly identified all infants that developed severe retinopathy of prematurity in this cohort. **Conclusions:** The ROPScore was useful to identify preterm babies at risk for retinopathy of prematurity. In this population, the ROPScore detected all patients at risk for any stage retinopathy of prematurity and severe retinopathy of prematurity. The ROPScore values in this study were similar to those previously described, thereby successfully validating the ROPScore for early detection of retinopathy of prematurity in very low birth weight preterm infants.

Keywords: Infant, premature; Retinopathy of prematurity; Very low birth weight; Risk factors; ROPScore; Severity of illness index; Blindness

INTRODUCTION

Retinopathy of prematurity (ROP) is a proliferative vitreoretinopathy of the retina, which occurs in preterm infants and is a major cause of childhood blindness that can be avoided[1,2]. ROP is a multifactorial disease with the most important risk factors being low birth weight (BW) and low gestational age (GA)[3]. Recently, low postnatal weight gain (WG) has also been determined as an important predictor for the development of ROP[4,5]. The ROPScore is based on cumulative risk factors for ROP and is useful for the early identification of patients who are at a greater risk for the development of ROP[4]. Additional to BW and GA, the ROPScore includes the use of oxygen therapy with mechanical ventilation, WG proportional to BW, as measured at postpartum week six, and the need for blood transfusions in order to identify infants early who are at a higher risk for ROP[6]. The ROPScore, as described by Eckert et al.[6] is a relatively simple method, since the information must be submitted only once at postpartum week six.

The ROPScore is not intended to replace the binocular indirect ophthalmoscopy examination performed by a well-trained ophthalmologist, which is the gold standard for the diagnosis of the disease, but rather to identify patients at a greater risk for the development of ROP and who will require more frequent ophthalmologic evaluations for effective and timely treatment. Hence, the aim of the present study was to evaluate the usefulness of the ROPScore to predict the occurrence of any stage of ROP and severe ROP in a population at risk for ROP in southern Brazil.

METHODS

The medical records of all very low birth weight (VLBW) preterm infants screened for ROP from August 2009 to December 2015 were retrospectively reviewed. This study was conducted at the Neonatal Intensive Care Unit (NICU) of the Darcy Vargas Maternity (MDV) and of the Jeser Amarante Faria Children's Hospital (HJAF) in Joinville, SC, Brazil. Both NICUs attend to patients from the Brazilian Public Health System. The study cohort included all VLBW preterm infants (BW at birth ≤1500 g and/or GA ≤32 weeks) who survived past the first ophthalmological examination performed between postpartum weeks four and six to postpartum week 42. Infants excluded were those with congenital ocular malformations and those transferred to another institution before the first ophthalmological examination or before postpartum week 42. Ophthalmological examinations were conducted in accordance with the Brazilian guidelines for screening and treatment of ROP under pupil dilation (with combined 2.5% phenylephrine and 0.5% tropicamide eye drops) and were repeated according to the findings from baseline examinations every one or two weeks until retinal vascularization was completed around postpartum week 42[7]. In case of ROP onset, examinations were performed at shorter time intervals. An oral 25% glucose solution was used to relieve any discomfort caused by the ocular examination[8]. Clinical outcomes included the occurrence of any stage of ROP and the development of severe ROP requiring treatment. Disease stage was recorded according to the International Classification of ROP form 1984/1987 and was revised in 2005 and the highest stage of ROP observed during the follow-up period was recorded[9-11]. Severe ROP was defined as disease stage 3-5 according to the Early Treatment for Retinopathy of Prematurity Randomized Trial[12]. Ophthalmological examinations were performed by the same ophthalmologist who was qualified for ROP screening (PZC).

Study approval

The study protocol was approved by the Research Ethics Committee of the Hans Dieter Schmidt Regional Hospital of the Secretary of State for Health of the State of Santa Catarina, according to the Resolution 466/2012 of the National Health Council (approval no. 30507514.5.0000.5363).

Statistical analysis

The sensitivity and specificity of the ROPScore values, as well as the positive predictive value (PPV), negative predictive value (NPV), and 95% confidence interval (CI) were calculated for any stage of ROP and severe ROP. All statistical analyses were performed using IBM SPSS Statistics for Windows software (version 23.0; IBM Corporation, Armonk, NY, USA).

RESULTS

The study cohort included 322 patients, with males accounting for 53.7% of the population (n=173). The majority of patients (82.6%) were of appropriate size for the GA (AGA), while five (1.6%) were large for the GA (BGA). The mean BW and GA of the entire cohort were 1181.8 ± 292.5 g and 29.5 ± 2.3 weeks, respectively. The mean WG of the entire cohort at postpartum week six was 479.5 ± 186.6 g (Table 1).

In the ROPScore ≥11 group, the mean score was 15.0 ± 2.2 and in the ROPScore ≥14.5, the mean score was 16.7 ± 1.2. As shown in table 2, the incidences of any stage of ROP and severe ROP in this study were 68.3% and 17%, respectively. Overall, 35 patients needed treatment for ROP stages 3-5. Of these patients, one had stage 4 disease and five had stage 5. As shown in table 3, 261 (81.1%) patients required oxygen therapy with mechanical ventilation, while 173 patients (53.7%) received blood transfusions.

The ROPScore ranged from 8.7 to 19.9. The best cutoff points for sensitivity and specificity were established as 11 for any stage of ROP and 14.5 for severe ROP[6]. For any stage of ROP, the sensitivity and specificity of the ROPScore were 98.6% (95% CI=97.9%-99.3%) and 35.3% (95% CI=32.3%-38.3%), respectively, with PPV of 76.6% (95% CI=74.0%-79.2%) and NPV of 92.3% (95% CI=90.6%-94.0%). For severe ROP, the sensitivity and specificity were 100% and 57.3% (95% CI=54.2%-60.4%), respectively, with a PPV of 22% (95% CI=19.4%-24.6%) and NPV of 100%. The cutoff values correctly identified all infants who developed severe ROP. Notably, the sensitivity of the ROPScore for severe ROP was 100%. In this group, the ROPScore correctly identified all patients with severe ROP.

Table 1. Demographic characteristics of the 322 study participants

	n (%)	Mean (min-max)	Standard deviation
Patients (n)	322		
Gender			
Male	173 (53.7)		
Female	149 (46.3)		
SGA	51 (15.8)		
AGA	266 (82.6)		
BGA	5 (1.6)		
BW (g)		1181.8 (550-2190)	292.5
GA (weeks)		29.5 (23-37)	2.3
WG 6th week (g)		479.5 (300-1200)	186.6
ROPScore (range)		14.4 (8.7-19.9)	2.6

AGA= appropriate for gestational age; BGA= big for gestational age; (min-max)= minimum-maximum; BW= birth weight; GA= gestational age; n= number of patients; ROP, retinopathy of prematurity; SGA= small for gestational age; WG= weight gain from birth to postpartum week 6.

Table 2. Demographic characteristics of the patients with ROPScores ≥11 and ≥14.5

	ROPScore ≥11 (mean ± SD)	ROPScore ≥14.5 (mean ± SD)
Patients (n)	283	157
BW (g)	1140.4 ± 275.1	990.3 ± 207.4
GA (weeks)	29.1 ± 2.2	27.8 ± 1.9
WG (g)	482.5 ± 189.5	475.1 ± 200.7
ROPScore (range)	15.0 ± 2.2	16.7 ± 1.2

BW= birth weight; GA= gestational age; n, number of patients; ROP= retinopathy of prematurity; WG= weight gain from birth to postpartum week 6 Data are presented as the mean ± standard deviation.

Table 3. Prevalence of ROP

ROP Stage	Number of patients (n=322)
Non-ROP patients	102 (31.7%)
ROP patients	220 (68.3%)
Stage 1	94 (29.2%)
Stage 2	91 (28.3%)
Stage 3*	29 (9%)
Stage 4*	1 (3%)
Stage 5*	5 (5%)

ROP= retinopathy of prematurity; *severe ROP= n, (%).

DISCUSSION

Over the past 10 years, several tools have been developed to predict the occurrence of ROP based on cumulative risk factors, such as WINROP (Weight, Insulin-like Growth Factor-1, Neonatal, ROP)[13,14], CHOP-ROP (Children's Hospital of Philadelphia)[15], ROPScore[6], and CO-ROP (The Colorado-ROP model)[16]. The WINROP study used the variables of GA, BW, weekly serum IGF-1

levels (when blood was collected for other reasons), and WG. Patient data were entered into a computer program indicating an alert for patients at risk for ROP if the measurements varied beyond the curve predicted by the program[13,14]. Over the years, through a less complex algorithm that was more acceptable by the NICU team, WINROP has been improved to allow for more accurate detection of patients at risk for severe ROP[17]. WINROP was validated in different countries, including Brazil[18]. CHOP-ROP is a score that also analyzes the risk of patients presenting with ROP that is associated with WG and uses the criteria of GA, BW, and daily weight measures that were inserted into an algorithm by the NICU team. This score does not use serum IGF-1 measurements. However, the requirement for daily weight makes it difficult to apply in clinical practice[15]. More recently, the CO-ROP to predict the occurrence of ROP in preterm infants is in the process of being validated[16].

ROPScore uses other criteria in addition to BW and GA. These other parameters are easily accessible, i.e., use of oxygen therapy with mechanical ventilation; WG proportional to BW measured at postpartum week six; the need for blood transfusions; and BW at postpartum week six. This last parameter is registered only once in a transversal way, thereby differing the ROPScore from all of the other algorithms that employ longitudinal diaries or weekly measures of BW[6].

Since the algorithm requires the entry of data only once, the ROPScore can be easily calculated before the first ophthalmological examination. In this way, it is relatively simple to identify following the first ophthalmological examination infants who are at a greater risk for the development of ROP. The higher the ROPScore, the greater the risk for the development of any stage of ROP and of severe ROP. The ROPScore is in the public domain and can be installed on any Microsoft Excel-compatible computer[6]. The score can be filled in by the NICU nurse and presented to the ophthalmologist in charge of the screening session, thereby facilitating its use in any NICU. The ROPScore was presented in two previous studies[6,19]. The epidemiological differences between the samples studied in Brazil and the populations of other countries suggest that the adjustment to the ROPScore cutoff points should be validated in different populations. For example, an Italian study revealed small differences from the results of a study by Eckert et al.[6], which showed significant statistical results, suggesting that the ROPScore may be an excellent tool in prediction of the risk for ROP[19]. The present study showed similar values to those described in both studies[6,19] performed in other centers that successfully validated the ROPScore for early detection of ROP in VLBW preterm infants. In the population studied, the ROPScore was able to detect all patients at risk of any stage of ROP and severe ROP.

The ROPScore should not be used to determine overall screening criteria, but rather to reduce the frequency of examinations in the same patient who is at risk for ROP. The ophthalmological examination conducted by a well-trained ophthalmologist using binocular indirect ophthalmoscopy in the NICU remains the gold standard for screening for diseases, as the ROPScore was not developed to replace ophthalmological examinations.

The ROPScore is a helpful algorithm to identify patients at a greater risk for the development of ROP who may require more frequent ophthalmologic evaluations and effective treatment. The greatest benefit of the ROPScore is the ability to avoid permanent and irreversible blindness. Hence, the ROPScore has emerged as an important tool that is both accessible and simple to use for the detection of patients who are at risk for ROP.

What was known before:

- Appropriate screening sessions for the detection of ROP are costly and create a heavy workload for the ophthalmologist. Repeated ophthalmological examinations may lead to stress and physical impairment in systemically compromised infants.

What this study adds:

- This study describes the use of the ROPScore in a southern Brazilian population of VLBW preterm infants who are at risk for ROP with the aim of reducing the excessive number of examinations needed to screen for ROP among VLBW infants.

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